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10/563,818	01/06/2006	Koji Suematsu	283148US0PCT	3729

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
03/11/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/563,818	SUEMATSU ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-37* is/are pending in the application.

4a) Of the above claim(s) *24,28 and 32-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,25-27 and 29-31* is/are rejected.

7)☒ Claim(s) *31* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of specie E (claim 30d) in the reply filed on January 12, 2009 is acknowledged. The traversal is on the ground(s) that no search burden was associated with searching all of the claimed polymorphisms. This is not found persuasive because each of these polymorphisms needs to be searched separately, and the Office allows one sequence search. Further, Applicants' statement that the election of primers cannot be made for the elected polymorphism because it was detected by RFLP results in withdrawal of claim 32 and all of claims depending from claim 32 from consideration. The requirement is still deemed proper and is therefore made FINAL.

2. Claims 24, 28 and 32-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 12, 2009.

3. Claims 23, 25-27 and 29-31 will be examined. Claim 30 will be considered with respect to the species (d).

4. Applicants' amendment filed 9/19/08 cancelled all of the previously pending claims, therefore all of the previously presented claim rejections and objections are withdrawn, and therefore Applicants' arguments are moot.

5. This office action presents new grounds for rejection.

Claim Objections

6. Claim 31 is objected to because of the following informalities: the period at the end of the claim is missing. Appropriate correction is required.

Incorporation by Reference

7. The attempt to incorporate subject matter into this application by reference to the GenBank Accession numbers on page 13 and 14 is ineffective because:

a) there is no statement that these accession numbers were incorporated by reference,

b) the versions of sequences AL162497 and XM_007095 that were used were not identified.

8. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 112, new matter

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 23, 25-27 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are rejected for the following reasons. The specification as originally filed did not provide a sequence listing or a description of where the polymorphisms in the IRS-2 gene are located. Specifically, Applicants state on page 13 and 14, paragraphs [0038]-[0039], that the IRS2 gene is included in the sequence with GenBank Accession No. AL162497, and the gene itself has accession No. XM_007095, and corresponds to bp 93,673-126,402 of the GenBank Accession No. AL162497. Applicants designated the positions of the polymorphic bases as follows (page 14, the end of the first paragraph):

"The position numbers of SNPs as described in the specification or the figure correspond to the position numbers counting from A of ATG that is used as a codon for Met at N-terminus of protein when mRNA is translated into protein (translation initiation codon)." Applicants did not indicate which bp of the XM_007095 is considered to be the A of the ATG codon.

Alignment of the sequences with GenBank Accession No. AL162497 and XM_007095 shows the following:

a) bp 1-3 of the cDNA for the IRS2 protein are "CGC", not "ATG".

b) Even if we assume that the numbering of SNPs starts with the first "C" (or G), there are still problems. For example, Fig. 1 indicates that the A29793G SNP is within exon 2. However, alignment of the cDNA for IRS2 and the AL162497 sequence indicates that exon 2 starts most likely at position 96,144 or 96,143. The bp 29,793 bp away from bp 126,402 would be bp 96,609, or about 450 bp away from exon 2. Further, bp 96,609 is an A on the strand shown, but a T on a complementary strand.

Applicants did not incorporate the two accession numbers by reference in the originally filed specification. Further, as shown in the attached GenBank revision histories for both of these sequences, the AL162497 sequence had 20 versions, and the XM_007095 sequence had six. Therefore, it is not clear what versions of the AL162497 sequence do SEQ ID NO: 18 and 19 correspond to. As indicated above, the positions of the polymorphisms were not clearly identified either with respect to the AL162497 sequence or the XM_007095 sequence; therefore, the base pair numbering in claim 30 does not have a clear origin in the disclosure as originally filed.

Therefore the claims contain new matter.

Claim Rejections - 35 USC § 112, written description

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 23, 25-27 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claim 23 is drawn to a method of linking the polymorphisms of the human insulin receptor substrate-2 (IRS2) gene to risk of granulocytopenia, where SEQ ID NO: 19 shows the gene sequence. The specification as originally filed did not provide a sequence listing or a description of where the polymorphisms in the IRS-2 gene are located. Specifically, Applicants state on page 13 and 14, paragraphs [0038]-[0039], that the IRS2 gene is included in the sequence with GenBank Accession No. AL162497, and the gene itself has accession No. XM_007095, and

corresponds to bp 93,673-126,402 of the GenBank Accession No. AL162497. Applicants designated the positions of the polymorphic bases as follows (page 14, the end of the first paragraph):

"The position numbers of SNPs as described in the specification or the figure correspond to the position numbers counting from A of ATG that is used as a codon for Met at N-terminus of protein when mRNA is translated into protein (translation initiation codon)." Applicants did not indicate which bp of the XM_007095 is considered to be the A of the ATG codon.

Alignment of the sequences with GenBank Accession No. AL162497 and XM_007095 shows the following:

a) bp 1-3 of the cDNA for the IRS2 protein are "CGC", not "ATG".

b) Even if we assume that the numbering of SNPs starts with the first "C" (or G), there are still problems. For example, Fig. 1 indicates that the A29793G SNP is within exon 2. However, alignment of the cDNA for IRS2 and the AL162497 sequence indicates that exon 2 starts most likely at position 96,144 or 96,143. The bp 29,793 bp away from bp 126,402 would be bp 96,609, or about 450 bp away from exon 2. Further, bp 96,609 is an A on the strand shown, but a T on a complementary strand.

Applicants did not incorporate the two accession numbers by reference in the originally filed specification. Further, as shown in the attached GenBank revision histories for both of these sequences, the AL162497 sequence had 20 versions, and the XM_007095 sequence had six. Therefore, it is not clear what versions of the AL162497 sequence do SEQ ID NO: 18 and 19 correspond to. As indicated above, the positions of the polymorphisms were not clearly identified either with respect to the AL162497 sequence or the XM_007095 sequence; therefore, the base pair numbering in claim 30 does not have a clear origin in the disclosure as originally filed.

Therefore, Applicants did not provide an adequate written description of the invention.

Claim Rejections - 35 USC § 112, enablement

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 23, 25-27 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 23, 25-27 and 29-31 are broadly drawn to methods of assessing the risk of drug-induced granulocytopenia by detecting a polymorphism of the human IRS2 receptor. However, as will be further discussed, there is no support in the specification and prior art for methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such

as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has a single working example in which subjects taking vesnarinone were examined for the presence of granulocytopenia associated with the drug and for polymorphisms in the IRS2 gene. Six polymorphisms, listed in Tables 1-6, were found to be significantly associated with the onset of granulocytopenia. No other patients subject to other therapeutic regimens were examined for polymorphisms in the IRS2 gene and their possible association with granulocytopenia.

Guidance in the Specification.

The specification provides no evidence that the disclosed six polymorphisms in the IRS2 would be indicative of the risk for granulocytopenia in patients taking drugs or drug combinations other than vesnarinone. Further, as detailed below, it is not clear where in the sequence of the IRS2 gene are these polymorphisms located.

The specification as originally filed did not provide a sequence listing or a description of where the polymorphisms in the IRS-2 gene are located. Applicants state on page 13 and 14, paragraphs [0038]-[0039], that the IRS2 gene is included in the sequence with GenBank Accession No. AL162497, and the gene itself has accession No. XM_007095, and corresponds to bp 93,673-126,402 of the GenBank Accession No. AL162497. Applicants designated the positions of the polymorphic bases as follows (page 14, the end of the first paragraph):

"The position numbers of SNPs as described in the specification or the figure correspond to the position numbers counting from A of ATG that is used as a codon for Met at N-terminus of protein when mRNA is translated into protein (translation initiation codon)." Applicants did not indicate which bp of the XM_007095 is considered to be the A of the ATG codon.

Alignment of the sequences with GenBank Accession No. AL162497 and XM_007095 shows the following:

a) bp 1-3 of the cDNA for the IRS2 protein are "CGC", not "ATG".

b) Even if we assume that the numbering of SNPs starts with the first "C" (or G), there are still problems. For example, Fig. 1 indicates that the A29793G SNP is within exon 2. However, alignment of the cDNA for IRS2 and the AL162497 sequence indicates that exon 2 starts most likely at position 96,144 or 96,143. The bp 29,793 bp away from bp 126,402 would be bp 96,609, or about 450 bp away from exon 2. Further, bp 96,609 is an A on the strand shown, but a T on a complementary strand. Therefore, the positions of the primers to amplify this polymorphism, as listed in Table 8 on page 53, as spanning bp 96,070-96,091 (SEQ ID NO: 14) and bp 96,209-96,190 (SEQ ID NO: 13), do not make sense.

Applicants did not incorporate the two accession numbers by reference in the originally filed specification. Further, as shown in the attached GenBank revision histories for both of these sequences, the AL162497 sequence had 20 versions, and the XM_007095 sequence had six. Therefore, it is not clear what versions of the AL162497 sequence do SEQ ID NO: 18 and 19 correspond to. As indicated above, the positions of the polymorphisms were not clearly identified either with respect to the AL162497 sequence or the XM_007095 sequence; therefore, the base pair numbering in claim 30 does not have a clear origin in the disclosure as originally filed.

The unpredictability of the art and the state of the art

No other references were found teaching or suggesting an association between granulocytopenia and IRS2 polymorphisms. However, three very recent references discuss a possible link between acquired granulocytopenia and polymorphisms in other genes. For example,

Berliner et al. (Hematology, vol. 2004, pp. 63-79, 2004; cited in the previous office action) discloses that in case of clozapine, tumor necrosis factor polymorphisms may play a role in the development of nutropenia (page 71, last two paragraphs; page 72, paragraphs 1-2 and Table 4).

Sugiyama et al. (J. Clin. Oncol., vol. 25, pp. 32-42, 2007; cited in the previous office action) examined the link between neutropenia caused by the anticancer drug gemcitabine in combination with carboplatin, cisplatin or fluorouracil, and polymorphisms in the cytidine deaminase (CDA) gene. They concluded that haplotype *3 was correlated with an increased risk for neutropenia in patients undergoing multiple drug therapy (Abstract; Table 2; page 37, fourth paragraph; Table 7; page 38, fourth paragraph).

Finally, Hahn et al. (Am. J. Health. Syst. Pharm., vol. 63, pp. 2211-2217, 2006; cited in the previous office action) teach that patients who are homozygous for the *28 allele of the uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) experience severe toxicity, including neutropenia (Abstract; page 2213, paragraphs 5-10; page 2214, first paragraph; Table 1).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to allow the use of polymorphisms in the IRS2 gene in the diagnosis of the risk of granulocytopenia. First, all possible polymorphisms would have to be examined in the IRS2 gene, and then population studies with numbers of patients large enough to produce statistically significant results would have to be conducted for every drug and drug combination currently in use in clinical practice to treat any disease and correlated with the presence and/or absence of certain IRS2 polymorphisms. This would require years of inventive

effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the development of granulocytopenia in patients depends on a total genetic makeup of the patient as well as on the type of disease and drug being taken, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112, second paragraph

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 23, 25-27 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23, 25-27 and 29-31 are indefinite in claim 23. Claim 23 is indefinite over the recitation of "wherein SEQ ID NO: 19 shows the polynucleotides of a human insulin receptor

substrate-2 gene". First, SEQ ID NO: 19 is much larger than the IRS-2 gene, therefore it is not clear what is the sequence of the IRS-2 gene with respect to SEQ ID NO: 19.

17. No references were found teaching or suggesting claims 23, 25-27 and 29, but they are rejected for reasons given above.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
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